

In the Specification:

Please amend the specification as follows:

In the drawings, please substitute the enclosed Replacement Sheets 1/7, 2/7, 3/7, 4/7, 5/7, 6/7, and 7/7 for the drawing sheets 1/8, 2/8, 3/8, 4/8, 5/8, 6/8, 7/8, and 8/8.

Please delete the paragraphs from the bottom of p 2 to the middle of p. 4, and replace them with the following paragraphs:

Therefore, according to a first aspect of the present invention, there is provided, an isolated substantially pure form of nucleic acid molecule encoding a human 5-HT_{4(h)} receptor. Preferably the 5-HT_{4(h)} receptor encoded by said nucleic acid molecule comprises the amino acid sequence illustrated in Figure 1B or a functional equivalent, derivative or bioprecursor of said receptor.

Thus, the present invention comprises a nucleic acid molecule encoding a human 5-HT_{4(h)} receptor or an immunologically and/or biologically active fragment thereof, which comprises a nucleotide sequence selected from the group consisting of:

- (a) nucleotide sequences encoding the amino acid sequence depicted in Figure 1B;
- (b) nucleotide sequences comprising the coding sequence as depicted in Figure 1A;
- (c) nucleotide sequences encoding a polypeptide derived from the polypeptide encoded by a nucleotide sequence of (a) or (b) by way of substitution, deletion and/or addition of one or several amino acids of the amino acid sequence encoded by the nucleotide sequence of (a) or (b);
- (d) nucleotide sequences the complementary strand of which hybridises with a nucleotide sequence of any one of (a) to (c);
- (e) nucleotide sequences encoding a polypeptide the amino acid sequence of which has an identity of 70% or more to

the amino acid sequence of the polypeptide encoded by a nucleotide sequence of any one of (a) to (d);

- (f) nucleotide sequences encoding a polypeptide capable of binding a ligand of 5-HT_{4(h)} comprising a fragment or an epitope-bearing portion of a polypeptide encoded by a nucleotide sequence of any one of (a) to (e);
- (g) nucleotide sequences comprising at least 15 consecutive nucleotides of a nucleotide sequence of any one of (a) to (f);
- (h) nucleotide sequences comprising a nucleotide sequence which is degenerated as a result of the genetic code to a nucleotide sequence of any of (a) to (g).

Advantageously, the isolated nucleic acid according to the invention may be used for expression in, for example, a host cell or the like using a suitable expression vector. Preferably, the nucleic acid may be a DNA molecule or a cDNA molecule. Preferably, the DNA molecule has the nucleic acid sequence as illustrated in Figure 1A.

Please delete the paragraphs relating to the Brief Description of the Figures, p 2 to p. 7, and replace them with the following paragraphs:

Brief Description of the Figures

The present invention may be more clearly understood from the following exemplary embodiment with reference to the accompanying figures wherein;

- Figure 1: A) is human 5-HT_{4(h)} (SEQ ID NO:1) The positions of primers used in this study are indicated by arrows and
- Figure 1: B) the amino acid sequences of human 5-HT_{4(h)} (SEQ ID NO:2).
- Figure 2: is an illustration of mRNA tissue distribution performed as described in Materials and Methods. The letters indicate the used primer combination in the PCR, A:FW AB1/REV B1 (5'part 5-HT₄ cDNA including h exon), B:FW AB1/REV AB2 (common part of all 5-HT₄ splice variants), C:FW AB2/REV SH1 (3'part 5-HT_{4a} cDNA), D:FW AB2/REV LO1 (3'part 5-HT_{4b} cDNA), E:FW B1/REV SH1 (3'part 5-HT₄ cDNA, combination of exon h and a), F:FWB1/REV LO1 (3'part 5-HT_{4(h)}).
- Figure 3: Saturation analysis of [³H]GR113808 binding on membrane preparation from COS-7 cells transfected with the h 5-HT_{4(h)}.
- Figure 4: Saturation analysis of [³H]5-HT binding on membrane preparation from COS-7 cells transfected with the h 5-HT_{4(h)}.
- Figure 5: Inhibition of specific [³H]GR113808 binding by 5-HT₄ agonist and antagonist. Membrane preparations from

COS-7 cells transiently transfected with h 5-HT_{4(h)} receptor were incubated with 0.25 nM [³H]GR113808. Non-specific binding was determined by 10 mM SB204070. Results are percentages, 100% is defined by specific binding in the absence of competing compound. Results are the mean of three independent experiments from three different transfections. Calculated pIC50 values are given in Table 1.

Figure 6:

Indirect estimation of AC stimulation by measuring cAMP formation in COS-7 cells transiently transfected with h 5-HT_{4(h)}. Results represent the increase of cAMP after stimulation by agonist since basal level has been removed. Results are the mean of three independent experiments from three different transfections. Calculated pEC50 and % of 5-HT_{max} values are given in Table 2. The efficacy and potency of the different agonists to trigger the cellular response was estimated and compared for the three different variants. The mean of pEC50 and the percentage of stimulation, normalized for the maximum stimulation induced by 5-HT (% of 5-HT maximum) for the h5-HT_{4(h)}, h5-HT_{4(a)} and h 5-HT_{4(b)}, are presented in Table 2. No difference in the pEC50 was noticed. The cAMP assay has been performed also for COS-7 cells transfected with the empty vector as a negative control. After stimulation with 10⁻⁶ M of each agonist, 5-HT, cisapride and prucalopride, no significant increase of the cAMP basal level was found.

Please delete the paragraph starting at the bottom of p 9 and continuing to p. 10, and replace it with the following paragraph:

Substantial homology preferably carries with it that the nucleotide and amino acid sequences of the 5-HT_{4(h)} of the invention comprise a nucleotide and amino acid sequence fragment, respectively, corresponding and displaying a certain degree of sequence identity to the sequences in Figure 1A and 1B. Preferably they share an identity of at least 30 %, preferably 40 %, more preferably 50 %, still more preferably 60 %, most preferably 70%, and particularly an identity of at least 80 %, preferably more than 90 % and still more preferably more than 95 % is desired with respect to the nucleotide or amino acid sequences depicted in Figures 1A and 1B, respectively. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using, for example, the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6 (1990), 237-245.) In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Further programs that can be used in order to determine homology/identity are described below and in the examples. The sequences that are homologous to the sequences described above are, for example, variations of said sequences which represent modifications having the same biological function, in particular encoding proteins with the same or substantially the same receptor specificity, e.g. binding specificity. They may be naturally occurring variations, such as sequences from other mammals, or mutations. These mutations may occur naturally or may be obtained by mutagenesis techniques. The allelic variations may be naturally occurring allelic variants as well as synthetically produced or genetically engineered variants. In a preferred embodiment the sequences are derived from a human.